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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary

Application No.

10/522,664

Applicant(s)

LENZ ET AL.

Examiner

Carla Myers

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 21 September 2007.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-15 is/are pending in the application.
- 4a) Of the above claim(s) 7-11 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-6 and 12-15 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 27 January 2005 is/are: a) ☒ accepted or b) ☐ objected to by the Examiner.
- Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
 - ☐ Certified copies of the priority documents have been received in Application No. _____.
 - ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- ☒ Notice of References Cited (PTO-892)
- ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- ☒ Information Disclosure Statement(s) (PTO/SB/08)
Paper No(s)/Mail Date 8/3/05, 1/11/06, 3/6/06, 2/5/07.
- ☐ Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____
- ☐ Notice of Informal Patent Application
- ☐ Other: _____

DETAILED ACTION

Election/Restrictions

1. Applicant's election without traverse of invention I and the species of fluoropyrimidine, colon/colorectal cancer and a polymorphism or genotype of ERCC1 in the reply filed on September 9, 2007 is acknowledged.

Claims 7-11 are withdrawn from consideration as being drawn to a non-elected invention. Claims 1-6 and 12-15 have been examined to the extent that the claims read on the elected subject matter.

Claim Objections

2. Claims 2-6 are objected to because the claims include subject matter of the non-elected inventions, namely the alternative therapy of a platinum drug (claims 2 and 4), the additional types of cancer (claim 3) and the additional genes (claims 5 and 6).

3. In claim 3, the claim appears to refer to the same species by two different names – i.e., colon cancer and colorectal cancer. Accordingly, the claims should be amended to refer to either colon cancer or to colorectal cancer.

4. In claim 12, "regimen is comprises the administration" should read "regimen comprises the administration."

Specification

5. The specification is objected to because the assigned SEQ ID NOs have not been used to identify each sequence listed, as required under 37 CFR 1.821(d). See, for example, page 44.

Claim Rejections - 35 USC § 112 Second Paragraph

6. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-6 and 12-15 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1-6 and 12-15 are indefinite because the claims do not recite a clear nexus between the preamble of the claims and the final process step of the claims. The claims are drawn to methods for selecting a therapeutic regimen for treating cancer. However, the final step is one for screening for a polymorphism or a genotype. Accordingly, it is unclear as to whether the claims are intended to be limited to methods for selecting a therapeutic regimen or methods for screening for a polymorphism or a genotype. In the former case, the claims omit essential process steps required to achieve the objective of selecting a therapeutic regimen because the claims do not set forth how the detection of a polymorphism or a genotype results in selection of a therapeutic regimen.

Claim 4 is indefinite over the recitation of "the cancer treatment" because this phrase lacks proper antecedent basis.

Claim 6 is indefinite over the recitation of "tissue sample is normal tissue that corresponds to the tumor type." The specification does not provide a definition for the term "corresponds" as it relates to tissues and tumors and there is no art recognized definition for this phrase with respect to tissues and tumors. The specification (page 3)

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provides an example of what might be encompassed by a tissue corresponding to a tumor, but does not teach that "corresponding" is limited to such an example. Thus, it is unclear as to what would be encompassed by a tissue that corresponds to a tumor type. Accordingly, one of skill in the art cannot determine the meets and bounds of the claimed subject matter.

Claims 6 and 14 are indefinite over the recitation that "the genotype is high expression of a gene." The specification (page 6) states that genotype refers to "the specific allelic composition of an entire cell or a certain gene, whereas the term "phenotype" refers to the detectable outward manifestation of a specific genotype." While a genotype may result in high expression of a gene, it is unclear as to what would be intended to be meant by a genotype being high expression of a gene. It is noted that the claims have been examined to the extent that they encompass a method of determining an allelic composition of a gene or cell. However, the claims must be amended to clarify the relationship between the genotype (allelic composition) and the occurrence of high expression of a gene. Further, claims 6 and 14 are indefinite over the recitation of "high expression" because this term is not defined in the specification and there is no art recognized definition for this term. It is unclear as to what would constitute high expression because the claims do not state what "high" is being compared to – e.g., any other mRNA or to mRNA in a control sample etc.

Claim Rejections - 35 USC § 112 – Written Description

7. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the

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art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-6 and 12-15 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a Written Description rejection.

In analyzing the claims for compliance with the written description requirement of 35 U.S.C. 112, first paragraph, the written description guidelines note that with regard to genus/species situations, a "Satisfactory disclosure of a "representative number" depends on whether one of skill in the art would recognize that the applicant was in possession of the necessary common attributes or features of the elements possessed by the members of the genus in view of the species disclosed." (See: Federal Register: December 21, 1999 (Volume 64, Number 244), revised guidelines for written description.)

To ascertain whether the written description requirement is met for a genus claim, it is first determined whether a representative number of species have been described by their complete structure. It is then determined whether a representative number of species have been defined by other identifying characteristics.

In the present situation, the claims are drawn to methods for selecting a therapeutic regimen by screening a patient sample for any genomic polymorphism or genotype. The specification (page 6) states that the term genotype refers to "the specific allelic composition of an entire cell or a certain gene." Thereby, the claims

encompass determining any alteration in a gene, including single or multiple nucleotide substitutions, deletions, insertions, translocations or chromosomal rearrangements in the genome of a patient as indicative of response to treatment for cancer. While claims 5, 6, and 14 are limited to methods wherein the genomic polymorphism or genotype is in the ERCC1 gene, claims 1-4, 12 and 15 encompass the determination of a polymorphism or genotype in any gene, such that the gene is not defined in terms of any structure or function. The claims encompass methods in which a polymorphism or genotype is detected in any patient, and thereby the claims encompass determining a polymorphism or genotype of any gene or of the ERCC1 gene in a human or any non-human organism. As discussed on page 9 of the specification, such organisms may include primates, sheep, goats, horses, dogs, cows, chickens, rats, frogs etc.

Accordingly, because the claims do not describe the polymorphisms or genotypes in terms of any structural features – such as the type of mutation or variation (insertion, deletion, substitution, translocation), number of nucleotides encompassed by the mutation/variation, the gene in which the polymorphism or genotype occurs (claims 1-4, 12 and 15), or the identity of the organism with respect to the ERCC1 gene (claims 5, 6 and 14), the claims encompass methods which detect a significantly large genus of polymorphism or genotypes in any organism.

With respect to the elected invention of the ERCC1 gene, this gene consists of 14,305bp and mutations are currently 83 mutations are known to be present in this gene in humans (see Gene Card for ERCC1 available via url: <genecards.org/cgi-bin/carddisp.pl?gene=ERCC1>).

However, the specification discloses only one polymorphism in the human ERCC1 gene – i.e., a C to T substitution at codon 118, which does not alter the amino acid sequence of the ERCC1 protein (see page 35). No additional single nucleotide polymorphisms or single or multiple insertions, deletions, substitutions, translocations or rearrangements in the human ERCC1 gene are disclosed. Further, no additional polymorphisms or genotypes in the ERCC1 gene of non-human organisms are disclosed. Additionally, the specification does not disclose the ERCC1 gene sequence of a representative number of non-human organisms and the occurrence of a C to T polymorphism at codon 118 in such ERCC1 gene sequences.

With respect to non-elected subject matter, the specification (page 31) also teaches a mutation in the human thymidylate synthase gene, wherein a 28bp sequence may be present as a double or triple tandem repeat downstream from the cap-site in the 5' regulatory region. Further, regarding the human GSTP1 gene, a G to A transition at nucleotide 313 of exon 5, resulting in an isoleucine to valine substitution at amino acid 105 is disclosed (page 40). Regarding the human EGFR gene, a dinucleotide CA repeat in intron 1 is disclosed (page 44), however, the location of the repeat in intron 1 is not provided. Regarding the human MMP-1 gene, the specification discloses the occurrence of a 3 polymorphisms in the promoter region – i.e., -1607 1G/2G; -1612 5A/6A; -1562 C/T (see page 49). Regarding the human IL-8 and CXCR1 genes, the specification discloses one polymorphism of a T-251A in the promoter region of IL-8 and one polymorphism in exon 2 (resulting in a Ser2607Thr alteration) in CXCR1 (see page 51).

Thereby, with respect to the elected invention, the specification has adequately described one polymorphism in the human ERCC1 gene – i.e., a C to T substitution at codon 118. However, the specification has not adequately described in terms of its complete structure any of the additional polymorphisms or genotypes in any organism required by the present claims, wherein said polymorphism or genotype is associated with response to cancer treatment. With respect to the non-elected subject matter, the specification discloses 8 mutations in the human TS, GSTP1, EGFR, MMP-1, IL-8 and CXCR1 genes. However, this disclosure does not constitute a representative number of polymorphisms or genotypes in each of these genes and in any gene in the human genome or in the genome of any non-human organism, wherein the polymorphism or genotype is correlated with response to cancer therapy.

Further, no additional members of the claimed genus have been sufficiently described in terms of any other relevant identifying characteristics (e.g. identity of the gene, location of an alteration in the gene, identity of the nucleotide or nucleotides which are altered, restriction site that is modified by the nucleotide alteration, etc).

Thus, applicant has established possession of only SEQ ID NO: 1, but did not have possession of a representative number of “additional mutations or variations” in a genus which comprises millions of different possibilities of insertions, deletions, and nucleotide substitutions.

Additionally, the specification does not disclose a clear structure-function relationship between the claimed polymorphisms/genotypes and their association with response to treatment with any chemotherapeutic drug. There is no showing or

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evidence which links a nucleotide sequence of the ERCC1 gene or a representative number of other genes with the function of response to any chemotherapeutic drug.

With respect to the ERCC1 gene, the specification (page 36) teaches that "(a) search of the literature failed to provide an explanation of how a "silent" polymorphism that results in a codon of lesser usage can be associated with higher levels of mRNA. Without being bound by any theory, Applicants note that this polymorphism is associated with ERCC1 mRNA levels and therefore can predict survival of patients with metastatic colorectal cancer treated with 5-FU/oxaliplatin." Thereby, even with respect to the single disclosed ERCC1 (T/C) polymorphism, a clear structure-function relationship is not set forth in the specification. No structure-function relationship is provided for any other potential polymorphisms or genotypes in the ERCC1 gene. In the absence of any clear structure-function relationship and in the absence of a representative number of species of the claimed genus, there is insufficient descriptive support for the currently claimed genus of any polymorphism or genotype correlated with response to any chemotherapeutic treatment.

The decisional law in this area has been very consistent. The Federal Circuit in Lilly, Fiers, Rochester and many other cases has determined that the written description issue applies to situations where the definition of the subject matter of the claims fails to provide description commensurate with the genus. The most recent case law directly supports this rejection. As the District Court in University of Rochester v. G.D. Searle & Co., Inc. (2003 WL 759719 W.D.N.Y., 2003. March 5, 2003.) noted "In effect, then, the '850 patent claims a method that cannot be practiced until one discovers a compound

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that was not in the possession of, or known to, the inventors themselves. Putting the claimed method into practice awaited someone actually discovering a necessary component of the invention." This is similar to the current situation since the breadth of the current claims comprises the detection of polymorphisms and genotypes which the present inventors were not in the possession of, or which were not known to the inventors. In a genus that is possibly quite immense, the specification discloses only methods which detect one polymorphism in the ERCC1 gene of humans (i.e., the C to T substitution in codon 118) as indicative of response to treatment with 5-FU/oxaliplatin therapy.

As noted in Vas-Cath Inc. v. Mahurkar (19 USPQ2d 1111, CAFC 1991), the Federal Circuit concluded that:

"...applicant must also convey, with reasonable clarity to those skilled in art, that applicant, as of filing date sought, was in possession of invention, with invention being, for purposes of "written description" inquiry, whatever is presently claimed."

Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. 112 is severable from its enablement provision.

With respect to the present invention, there is no record or description which would demonstrate conception of a representative number of polymorphisms or genotypes in the ERCC1 or any other gene, of any organism, wherein the polymorphisms and genotypes are correlated with response to any chemotherapeutic treatment. Therefore, the claims fail to meet the written description requirement because the claims encompass a significantly large genus of polynucleotide sequences which are not described in the specification.

Claim Rejections - 35 USC § 112 - Enablement

8. Claims 1-6 and 12-15 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for methods for predicting the survival of a human patient having metastatic colon cancer, the method comprising: i) obtaining a nucleic acid sample from colon cancer tissue or colon cancer cells of a human patient having metastatic colon cancer and treated with 5-fluoropyrimidine (5-FU) and oxaliplatin, wherein the nucleic acid sample comprises ERCC1 nucleic acids; ii) analyzing the sequence of the ERCC1 nucleic acids to determine the nucleotides present at codon 118; and iii) determining that the patient will have a longer survival following treatment with 5-FU and oxaliplatin if the patient has a C/C genotype at codon 118 of ERCC1, as compared to patients having a C/T or T/T genotype at codon 118 of ERCC1, does not reasonably provide enablement for methods which select any therapeutic regimen in any subject having any type of cancer by assaying for any polymorphism or genotype of the ERCC1 gene or any other gene. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The following factors have been considered in formulating this rejection (*In re Wands*, 858F.2d 731, 8 USPQ2d 1400 (Fed. Cir. 1988): the breadth of the claims, the nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability or unpredictability of the art, the amount of direction or guidance presented, the presence or absence of working examples of the invention and the quantity of experimentation necessary.

Breadth of the Claims:

The claims are drawn to methods for selecting a therapeutic regimen by screening a patient sample for any genomic polymorphism or genotype. The specification (page 6) states that the term genotype refers to "the specific allelic composition of an entire cell or a certain gene." Thereby, the claims encompass determining any alteration in a gene, including single or multiple nucleotide substitutions, deletions, insertions, translocations or chromosomal rearrangements in the genome of a patient as indicative of response to treatment for cancer. While claims 5, 6, and 14 are limited to methods wherein the genomic polymorphism or genotype is in the ERCC1 gene, claims 1-4, 12 and 15 encompass the determination of a polymorphism or genotype in any gene, such that the gene is not defined in terms of any structure or function. The claims encompass methods in which a polymorphism or genotype is detected in any patient, and thereby the claims encompass determining a polymorphism or genotype of any gene or of the ERCC1 gene in a human gene or a gene from any organism. As discussed on page 9 of the specification, such organisms may include primates, sheep, goats, horses, dogs, cows, chickens, rats etc.

The claimed genus of polymorphisms and genotypes is considered to be significantly large. With the exception of claim 13, the claims do not describe the polymorphisms or genotype in terms of any structural features – such as the type of mutation or variation (insertion, deletion, substitution, translocation), number of nucleotides encompassed by the mutation/variation, the gene in which the polymorphism or genotype occurs (claims 1-4, 12 and 15), or the identity of the

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organism with respect to the ERCC1 gene (claims 5, 6 and 14). The ERCC1 gene consists of 14,305bp and mutations are currently 83 mutations are known to be present in this gene in humans (see Gene Card for ERCC1 available via url: genecards.org/cgi-bin/carddisp.pl?gene=ERCC1). The human genome comprises at least 20,000 to 25,000 genes. The genomes of all other organisms comprise millions of genes when considered together. Thereby, the claims encompass the detection of a phenomenally large genus of polymorphisms and genotypes (single and multiple nucleotide substitutions, deletions, insertions, repeats, translocations and rearrangements) present in the ERCC1 gene or in any other gene. Only one polymorphism (the C to T substitution at codon 118 of ERCC1) has been described in terms of its structure (nucleotide identity and location).

The claims further include detecting a polymorphism or genotype by any means, including methods wherein the polymorphism or genotype are indirectly detected by assaying for an unspecified polymorphism or genotype that is in linkage disequilibrium, or by assaying for an unspecified biological activity.

The claims also include detecting a polymorphism or genotype in any organism.

The claims include detecting a polymorphism or genotype that is correlated with response to any treatment, wherein the treatment may be any chemotherapy, including treatment with any type of fluoropyrimidine drug or platinum drug.

The claims include detecting a polymorphism or genotype that is correlated with any type of treatment outcome – e.g., tumor regression, time of survival, reduction in

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time of cancer recurrence, or a decrease in cancer metastasis (see page 9 of the specification).

The claims include assaying any type of biological sample for the occurrence of a polymorphism or genotype.

Nature of the Invention

The claims are drawn to methods for selecting a therapeutic regimen by screening a patient sample for any genomic polymorphism or genotype. The invention is in a class of inventions which the CAFC has characterized as 'the unpredictable arts such as chemistry and biology' (Mycogen Plant Sci., Inc. v. Monsanto Co., 243 F.3d 1316, 1330 (Federal Circuit 2001)).

Teachings in the Specification and State of the Art:

With respect to the elected invention of the ERCC1 gene, the specification discloses only one polymorphism in the human ERCC1 gene – i.e., a C to T substitution at codon 118, which does not alter the amino acid sequence of the ERCC1 protein (see page 35). The specification further teaches the results of a genotyping study of intratumor tissues obtained from 60 metastatic colon cancer patients that received 5-FU/oxaliplatin chemotherapy (pages 34-36). It is stated that patients with the C/C genotype had a median survival of 531 days, whereas the median survival for patients with the C/T and T/T genotypes was 254 days and 256 days, respectively (page 36).

Regarding the prior art, the specification (page 35) teaches:

Studies have shown that increased ERCC1 mRNA levels are directly related to clinical resistance to cisplatin in human ovarian cancer as well as cervical cancer. It has previously been shown that ERCC1 mRNA levels are also directly correlated to clinical resistance to 5-FU and cisplatin in gastric cancer patients. It

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has also recently been shown that intra-tumoral ERCC1 mRNA levels are able to predict clinical response and overall survival in patients with metastatic colorectal cancer treated with 5-FU/oxaliplatin.

The specification (page 35) also teaches that the presence of the T/T and T/C genotypes are correlated with higher levels of ERCC1 mRNA. It is stated that the median ERCC1 mRNA level is 2.95, and that 27.3% of patients with the C/C genotype had mRNA levels greater than 2.95, whereas 41.7% and 77.8% of patients with the C/T and T/T genotype had mRNA levels greater than 2.95. Thus, the specification (page 35) concludes that When the mRNA levels of patients containing the C allele was compared to those without the C allele, the difference was statistically significant ($p=0.049$).

With respect to non-elected subject matter, the specification (page 31) also teaches a mutation in the human thymidylate synthase gene, wherein a 28bp sequence may be present as a double or triple tandem repeat downstream from the cap-site in the 5' regulatory region. Further, regarding the human GSTP1 gene, a G to A transition at nucleotide 313 of exon 5, resulting in an isoleucine to valine substitution at amino acid 105 is disclosed (page 40). Regarding the human EGFR gene, a dinucleotide CA repeat in intron 1 is disclosed (page 44), however, the location of the repeat in intron 1 is not provided. Regarding the human MMP-1 gene, the specification discloses the occurrence of a 3 polymorphisms in the promoter region – i.e., -1607 1G/2G; -1612 5A/6A; -1562 C/T (see page 49). Regarding the human IL-8 and CXCR1 genes, the specification discloses one polymorphism of a T-251A in the promoter region of IL-8 and

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one polymorphism in exon 2 (resulting in a Ser2607Thr alteration) in CXCR1 (see page 51).

The Predictability or Unpredictability of the Art :

The specification (page 35) identifies only one polymorphism in the human ERCC1 gene (the C to T substitution at codon 118 of exon 4) and states that the C/C genotype is correlated with increased survival in metastatic colon cancer patients treated with 5-FU/oxaliplatin. The art of identifying additional polymorphisms and genotypes correlated with response to drug treatment in cancer patients is highly unpredictable. Knowledge that a polymorphism exists does not allow one to conclude that the polymorphism is associated with a phenotype, such as response to treatment. Further, knowledge that a polymorphism is associated with one phenotype, such as survival following 5-FU/oxaliplatin treatment, does not allow one to conclude which, if any, additional phenotypes (survival in response to other chemotherapeutic agents; cancer regression, reduction in metastasis etc) will also be associated with the presence of the polymorphism or combination of polymorphisms.

In particular, it is highly unpredictable as to what would be the identity of additional polymorphisms in the ERCC1 gene or in other unspecified genes that could be used to select a therapeutic regimen to treat cancer. The genus of genes, and polymorphisms in genes, that may be correlated with any type of response to any chemotherapeutic agent is incredibly large. The specification does not disclose a representative number of these polymorphisms or genotypes that could be used to select a therapeutic regimen.

The unpredictability of establishing an association between a polymorphism and a phenotype is well accepted in the art. For example, Hirschhorn et al. (Genetics in Medicine. 2002. 4(2): 45-61) teaches that most reported associations between genetic variants and phenotypes are not robust. Hirschhorn states that "of the 166 putative associations studied three or more times, only 6 have been consistently replicated" (see abstract). The reference sets forth a number of reasons for the irreproducibility of these studies, suggesting that population stratification, linkage disequilibrium, gene-gene or gene-environment interactions, and weak genetic effects and lack of power are possible factors that lead to such irreproducibility. Hirschhorn concludes that "the current irreproducibility of most studies should raise a loud cautionary alarm" (page 60, col. 2). Thus, Hirschhorn cautions in drawing conclusions from a single report of an association between a genetic variant and disease susceptibility.

The unpredictability of identifying additional variants of ERCC1 correlated with response to treatment is supported by the post-filing date art of Winter (Oncogene. 2005. 24: 2110-2113). Winter discloses a mutation in exon 1 of ERCC1, resulting in a differentially spliced variant of ERCC1. It is stated that this variant has been previously disclosed as being associated with ERCC1 mRNA levels (page 2110). However, Winter found that the variant and wildtype ERCC1 transcripts were present at similar ratios in the tissues examined. Winter (page 2111) states that this data does not support the conclusion that the polymorphism leading to the alternatively spliced transcript is associated with ERCC1 mRNA levels. Winter (page 211s) also teaches that the

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alternatively spliced transcript is present in both normal and cancer cells and does not appear to be related to the occurrence of cancer.

It is also highly unpredictable as to whether the results obtained with survival of metastatic colon cancer patients following 5-FU/oxiplatin treatment can be extrapolated to other treatment regimens and other types of outcomes.

The unpredictability of extrapolating the results obtained with the codon 118 polymorphism to other types of outcomes and responses to other chemotherapeutic agents is emphasized by the teachings of Yu et al. (Mutation Research. 1997. 382: 13-20). Yu (Table 2 and page 19) found that the 118 AAT and AAC codons were present in both ovarian cancer tissues that were sensitive to cisplatin treatment and in ovarian cancer tissues that were resistant to cisplatin treatment. Yu did not observe an association between the occurrence of the C/C, C/T or T/T genotypes and response to cisplatin in ovarian cancer patients. This unpredictability is also supported by the teachings of Lee (Proceedings American Association Cancer Research. 2005. 46: Abstract 1496) wherein it is disclosed that expression levels of ERCC1 are not correlated with survival following cisplatin-based adjuvant therapy in resected gastric cancer.

The teachings of Grau (Journal of Clinical Oncology. 2005. 23: 511S) also support the finding of unpredictability in the art. Grau teaches that in oropharyngeal carcinoma patients, the ERCC1 118 codon polymorphism was not correlated with response to cisplatin/5-FU therapy.

The teachings of Kang (Experimental and Molecular Medicine. 2006. 38: 320-324) also emphasizes the unpredictability in the art, particularly with respect to extrapolating the findings obtained with the codon 118 polymorphism and response to other types of treatment in other types of cancers. Kang reports that the C/T and T/T genotypes were correlated with reduced risk of platinum-resistance in ovarian cancer. However, no significant association was observed between the ERCC1 polymorphism and overall survival in ovarian cancer patients treated with platinum-based drugs (see abstract and page 323). Further, Kang states that, as of 2006, the mechanism by which the ERCC1 polymorphism effects response to chemotherapy remains unclear. It is stated that "functional data supporting the association between the ERCC1 polymorphism and its activity are still controversial and insufficient" (page 323).

The unpredictability of extrapolating the results obtained with the codon 118 polymorphism to response to other chemotherapies is also supported by the post-filing date art of Viguiet (Clinical Cancer Research. 2005. 11: 6212-6217). Viguiet teaches that while the codon 118 T/T genotype was associated with response of metastatic colorectal cancer patients to 5-FU/oxiplatin, the T/T, C/T and C/C genotypes were not associated with response to 5-FU alone or 5-FU in combination with irinotecan (page 6215). The reference (page 6216) teaches that the lack of association between the ERCC1 polymorphism and response to 5-FU therapy "is not surprising because ERCC1 is unlikely to play a role in the repair of 5-FU-induced lesions." Moreover, Viguiet (page 6216) teaches the unpredictability of indirectly assaying for the codon 118 mutation by assaying for expression levels. Specifically, the reference teaches that it is difficult to

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measure ERCC1 protein levels "because the experiments undertaken to define ERCC1 protein expression using immunohistochemical techniques were not judged reliably enough." Also, methods which assay for ERCC1 mRNA levels are unpredictable because the mRNA "can be quantified only in fresh tumors that are handled in conditions allowing high-quality RNA isolation to perform quantitative reverse transcription-PCR."

The unpredictability of assaying for alternative genotypes as indicative of response to treatment is supported by the teachings of Yu (Cancer Letters. 2000. 151: 127-132). Yu (2000) reported that the ERCC1 mRNA levels are correlated with clinical resistance to platinum-based therapy in ovarian cancer and gastric carcinoma (page 128, col. 1). The reference teaches that in human gliomas, a change in ERCC1 copy number is frequently observed. However, Yu (page 131) found that ERCC1 allelic loss or gain is not associated with response to cisplatin treatment, and thereby does not appear to account for the change in ERCC1 mRNA levels in cancer patients sensitive or resistant to cisplatin therapy.

Additionally, Britten (International Journal of Cancer. 2000. 89: 453-457) teaches that ERCC1 protein levels are not correlated with cisplatin resistance in cervical tumors. Britten concludes that the association between ERCC1 mRNA levels and cancer may be an epiphenomenon, i.e., "mRNA levels may be a surrogate marker for some other determinant of response to chemotherapy in these cells" (see page 456).

It is also unpredictable as to whether a particular polymorphism must be present as homozygous or heterozygous, in order to be associated response to treatment.

It is unpredictable as to whether the results obtained with humans can be extrapolated to other organisms. This unpredictability is supported by the teachings of Halushka (Nature, July 1999, 22: 239-247). Halushka studied the frequency of polymorphisms among different ethnic populations and between human and apes. The reference (see abstract, page 244 col. 2 and page 245, col 1) found that there was considerable diversity in the number and frequency of SNPs between different ethnic groups and between humans and orthologous great ape sequences.

It is also unpredictable as to whether samples other than intratumoral colorectal cancer samples can be analyzed for the presence of the codon 118 C to T polymorphism as indicative of survival following 5-FU/oxiplatin therapy. The specification (page 35) teaches only the results of a study obtained using intratumoral samples. It is well known in the art that mutations arise spontaneously in tumor samples, such that a polymorphism present in normal tissue may not be present in a tumor tissue and vice versa. Since it is the tumor itself that responds to the treatment, the presence or absence of a the polymorphism in non-tumor tissue does not predict the occurrence the same polymorphism in cancer tissue or the response of a patient to chemotherapy. The specification does not provide any data on the presence of the ERCC1 codon 118 polymorphism in normal tissue and response of a patient to 5-FU/oxiplatin therapy or any other therapy.

Amount of Direction or Guidance Provided by the Specification and Degree of Experimentation:

The specification does not provide sufficient guidance as to how to detect additional polymorphism or genotypes in the ERCC1 gene or in other genes as indicative of response to any therapy. Extensive experimentation would be required to identify individual polymorphisms and genotypes. For example, such experimentation may involve sequencing the 14,305 nucleotides of the ERCC1 gene of individuals that are sensitive to 5-FU/oxiplatin treatment, sequencing the ERCC1 gene of individuals that are resistant to 5-FU/oxiplatin treatment, determining the frequency of any polymorphisms that are present in the individuals resistant to treatment and not present in individuals sensitive to treatment, or vice versa, that do not have diabetes, performing a statistical analysis to determine whether there is a statistically significant increase or decrease in the occurrence of a novel polymorphism in individuals sensitive to 5-FU/oxiplatin treatment. Additional experimentation would require performing this type of analysis in a representative number of non-human organisms. Further experimentation would require performing the above analysis in a representative number of additional genes in the human genome and the genomes of non-human organisms. Additionally, the experimentation may include performing the above methods in patients treated with a representative number of additional chemotherapeutic agents, including any fluoropyrimidine compound or platinum compound. The outcome of such experimentation cannot be predicted and is thus considered to be undue.

While methods for sequencing nucleic acids are known in the art, such methods provide only the general guidelines that allow researchers to randomly search for

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polymorphisms that may be linked to a particular phenotype, such as response to chemotherapy. The results of performing such methodology are highly unpredictable. The specification has provided only an invitation to experiment. The specification does not provide a predictable means for identifying additional polymorphisms and genotypes of ERCC1 or other genes associated with response to therapy.

Additionally, the specification does not provide sufficient guidance as to how to practice a method wherein a polymorphism or genotype is indirectly assayed for by, for example, detecting an allele that is in linkage disequilibrium with the codon 118 polymorphism or any other polymorphism. The specification does not identify any specific polymorphisms that are in linkage disequilibrium with codon 118 polymorphism and which are correlated with response to therapy. The specification also does not provide sufficient guidance as to how to perform any type of activity assay to indirectly detect the presence of the codon 118 polymorphism or any polymorphism or genotype in any other gene.

The specification does not provide sufficient guidance to enable the skilled artisan to extrapolate the findings obtained with survival response following 5-FU/oxiplatin treatment in patients having metastatic colon cancer to other outcomes following other types of treatment. The specification does not provide a clear structure-function relationship between the codon 118 polymorphism and response to therapy that would allow one to predictably extrapolate the findings obtained with 5-FU/oxiplatin therapy to other therapies. As stated in the specification (page 36) "(a) search of the literature failed to provide an explanation of how a "silent" polymorphism that results in a

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codon of lesser usage can be associated with higher levels of mRNA. Without being bound by any theory, Applicants note that this polymorphism is associated with ERCC1 mRNA levels and therefore can predict survival of patients with metastatic colorectal cancer treated with 5-FU/oxaliplatin." Thereby, even with respect to the single disclosed ERCC1 (T/C) polymorphism, a clear structure-function relationship is not set forth in the specification. No structure-function relationship is provided for any other potential polymorphisms or genotypes in the ERCC1 gene or in a representative number of additional genes in the human genome or genome of other organisms.

Working Examples:

The specification provides a working example in which a correlation between the presence of the C/C genotype and survival in metastatic colorectal cancer patients following treatment with 5-FU/oxiplitin.

No working examples are provided in which the presence of the codon 118 ERCC1 mutation is correlated with response to other types of treatment or is correlated to other clinical outcomes following treatment.

No working examples are provided in which a representative number of additional polymorphisms or genotypes in the ERCC1 gene are detected as indicative of response to therapy.

No working examples are provided wherein polymorphisms in the ERCC1 gene or in any other gene are detected in a representative number of non-human organisms as indicative of response to therapy.

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No working examples are provided in which the codon 118 ERCC1 polymorphism is specifically indirectly detected by assaying for an alternative polymorphism/mutation or by performing a biological activity assay.

Conclusions:

Case law has established that '(t)o be enabling, the specification of a patent must teach those skilled in the art how to make and use the full scope of the claimed invention without 'undue experimentation.'" *In re Wright* 990 F.2d 1557, 1561. *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970) it was determined that '(t)he scope of the claims must bear a reasonable correlation to the scope of enablement provided by the specification to persons of ordinary skill in the art". The amount of guidance needed to enable the invention is related to the amount of knowledge in the art as well as the predictability in the art. Furthermore, the Court in *Genetech Inc. v Novo Nordisk* 42 USPQ2d 1001 held that '(l)t is the specification, not the knowledge of one skilled in the art that must supply the novel aspects of the invention in order to constitute adequate enablement".

In the instant case, the specification has not enabled one of skill the art to practice the invention as it is broadly claimed because the specification does not teach a representative number of polymorphisms or genotypes in the ERCC1 gene or in other genes of the human genome or in the genomes of non-human organisms which are correlated with response to any type of cancer therapy. Accordingly, although the level of skill in the art of molecular biology is high, given the lack of disclosure in the specification and in the prior art and the unpredictability of the art, it would require

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undue experimentation for one of skill in the art to make and use the invention as broadly claimed.

Double Patenting

9. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-6, and 12-15 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-7 and 14-22 of copending Application No. 11/173,889. Although the conflicting claims are not identical, they are not patentably distinct from each other because the present claims and the claims of '889 are both inclusive of methods for selecting a therapeutic regimen for treating cancer comprising screening a cell or tissue sample from a patient for a genomic polymorphism or genotype. In particular, the present claims and the claims of '889 are both inclusive of methods in which the cancer is colon cancer and the

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treatment is 5-FU and oxaliplatin. While the claims of '889 do not specifically recite the detection of the codon 118 C to T polymorphism in ERCC1, when read in light of the specification of '889, it is clear that the broad recitation of any polymorphism or genotype is intended to encompass the codon 118 C to T polymorphism in the ERCC1 gene (see, e.g., para [0279] and [0280] of '889)

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

10. Claims 1-4, 12 and 15 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 47, 48, 52, 53, 56, 61-66, and 68-70 of copending Application No. 09/715,764. Although the conflicting claims are not identical, they are not patentably distinct from each other. The present claims are drawn generically to methods for selecting a therapeutic regimen for treating cancer comprising screening a cell or tissue sample from a patient for a genomic polymorphism or genotype. The claims of '764 are drawn to methods for identifying colorectal cancer patients sensitive to TS-directed chemotherapy by assaying for the polymorphism of double repeat of the 28bp repeat sequence in the 5' UTR of the TS gene. Accordingly, the claims of '764 are drawn to methods for detecting a polymorphism which is correlated with response to cancer therapy, as is encompassed by the present claims. Thereby, the present claims are generic to all that is recited in the claims of '764. Regarding present claim 2, the claims of '764 are directed to methods which detect the TS repeat sequence polymorphism as indicative of response to 5-FU. With respect to claim 4, the colorectal cancer disclosed by the claims of '764 can be

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further treated with radiation. constitutes the detection. With respect to present claims 12 and 15, the claims do not require an active step of administering 5-FU/oxaliplatin and do not require a specific step in which 5-FU/oxaliplatin is selected for treatment. Accordingly, the recitation that the therapeutic regimen comprises administering 5-Fu and oxaliplatin is not considered to further limit the claims.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

11. Claims 1-4, 12 and 15 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-20 of copending Application No. 11/691,670. Although the conflicting claims are not identical, they are not patentably distinct from each other. The present claims are drawn generically to methods for selecting a therapeutic regimen for treating cancer comprising screening a cell or tissue sample from a patient for a genomic polymorphism or genotype. The claims of '670 are drawn to methods for identifying patients suffering from gastrointestinal cancer that is suitably treated with a therapy comprising assaying for the presence of a SCN1A_T107\67A_SNP T/T polymorphism in the VGSC gene as indicative of a suitable response to therapy. Accordingly, the claims of '670 are drawn to methods for detecting a polymorphism which is correlated with response to cancer therapy, as is encompassed by the present claims. Thereby, the present claims are generic to all that is recited in the claims of '670. Regarding present claim 2, the claims of '670 are directed to methods which detect the polymorphism as indicative of response to 5-FU. With respect to claim 4, the colorectal cancer disclosed by the claims

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of '670 can be further treated with radiation. With respect to present claims 12 and 15, the claims do not require an active step of administering 5-FU/oxaliplatin and do not require a specific step in which 5-FU/oxaliplatin is selected for treatment. Accordingly, the recitation that the therapeutic regimen comprises administering 5-FU and oxaliplatin is not considered to further limit the claims.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

12. Claims 1-4, 12 and 15 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-11 of copending Application No. 11/681,615. Although the conflicting claims are not identical, they are not patentably distinct from each other. The present claims are drawn generically to methods for selecting a therapeutic regimen for treating cancer comprising screening a cell or tissue sample from a patient for a genomic polymorphism or genotype. The claims of '615 are drawn to methods for identifying patients having cancer that will response to anti-VEGF based chemotherapy by assaying for a polymorphism or genotype selected from IL-18 -251, VEGF 936, and AM 3' CA repeats. Accordingly, the claims of '615 are drawn to methods for detecting a polymorphism which is correlated with response to cancer therapy, as is encompassed by the present claims. Thereby, the present claims are generic to all that is recited in the claims of '615. Regarding present claim 2, the claims of '615 include methods in which the patient has colon cancer, which is a cancer that can be treated with a fluoropyrimidine. Regarding claim 4, the colorectal cancer recited by the claims of '615 can be further treated with radiation.

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With respect to present claims 12 and 15, the present claims do not require an active step of administering 5-FU/oxaliplatin and do not require a specific step in which 5-FU/oxaliplatin is selected for treatment. Accordingly, the recitation that the therapeutic regimen comprises administering 5-FU and oxaliplatin is not considered to further limit the claims.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claim Rejections - 35 USC § 102

13. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-6 and 12-15 are rejected under 35 U.S.C. 102(b) as being anticipated by Yu et al. (Mutation Research. 1997. 382: 13-20).

As noted in the MPEP 211.02, “a preamble is generally not accorded any patentable weight where it merely recites the purpose of a process or the intended use of a structure, and where the body of the claim does not depend on the preamble for completeness but, instead, the process steps or structural limitations are able to stand alone.” Further, in *Pitney Bowes Inc. v. Hewlett-Packard Co.*, 182F.3d 1298, 1305, 51 USPQ2d 1161, 1166 (Fed Cir. 1999) the court held that if the body of the claim sets forth the complete invention, and the preamble is not necessary to give “life, meaning and vitality” to the claim, “then the preamble is of no significance to claim construction

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because it cannot be said to constitute or explain a claim limitation". In the present situation, the claim language of "for selecting a therapeutic regimen for treating a cancer" is a statement of purpose and intended result and does result in a manipulative difference in the method steps of the claims. Accordingly, the process steps are able to stand alone and therefore the preamble limitation is not accorded patentable weight. Thus, the claims have been interpreted as being limited to methods comprising screening a cell or tissue sample from a patient for a genomic polymorphism or genotype, wherein it is a property of the polymorphism or genotype that it is correlated with treatment outcome of cancer.

Yu teaches a method comprising obtaining a tissue sample (ovarian cancer tissue and normal ovarian tissue) from a patient having ovarian cancer and assaying the tissue sample for the presence of a T or a C at codon 118 in exon 4 of the ERCC1 gene (page 14, col. 2 through page 15, col. 1). Accordingly, Yu anticipates the claimed invention.

Regarding claim 2, ovarian cancer is a cancer that can be treated with fluoropyrimidine.

Regarding claims 3, and 2-15, as stated above, the preamble of the claims is not considered to further limit the claims. Accordingly, the claims do not require that the patient from which the sample has been isolated has colon cancer. Rather, the claims require only screening for a polymorphism in a patient. Regarding claim 4, ovarian cancer is a cancer that can also be treated with radiation therapy.

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Regarding claims 5, 13 and 15, Yu teaches that the 118 C to T polymorphism is detected in the ERCC1 gene (page 14, col. 2).

Regarding claims 6 and 14, the claims do not set for the relationship between the polymorphism and high expression of a gene. As discussed in paragraph 6 above, a genotype is considered to be limited to an allelic composition of a cell or gene. Additionally, the claims do not require performing a step in which high gene expression is detected by, for example, determining the quantity of a mRNA. Accordingly, it has been interpreted that the claims are inclusive of a method for detecting a polymorphism or genotype, wherein the polymorphism or genotype is correlated with high expression of a gene. In the present situation, it is considered to be a property of the ERCC1 C to T polymorphism that it is associated with high expression of ERCC1.

Further, regarding claims 12 and 15, the claims do not require an active step of administering 5-FU/oxaliplatin and do not require a specific step in which 5-FU/oxaliplatin is selected for treatment. Accordingly, the recitation that the therapeutic regimen comprises administering 5-Fu and oxaliplatin is not considered to further limit the claims.

Regarding claim 15, it is considered to be a property of the ERCC1 C to T polymorphism at codon 118 that it is associated with the probability of recurrence free survival.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Carla Myers whose telephone number is 571-272-0747. The examiner can normally be reached on Monday-Thursday (6:30-5:00).

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If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached on 571-272-0735. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Carla Myers/

Primary Examiner, Art Unit 1634